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Low Urinary Cortisol Excretion in Patients with Posttraumatic Stress Disorder

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In the present study, we replicated and extended our previous findings of low urinary free-cortisol levels in PTSD. Cortisol was measured in 16 male patients (nine inpatients, seven outpatients) with posttraumatic stress disorder (PTSD) and in 16 nonpsychiatric control subjects. The mean cortisol level in the PTSD group was significantly lower, and the range narrower, than that observed in control subjects. Low cortisol in PTSD did not seem to be related to the presence or absence of major depressive disorder or to overall psychiatric symptomatology as assessed by the sum Brief Psychiatric Rating Scale score. In the outpatient group, there was a relationship between PTSD symptomatology and cortisol levels. The findings suggests a physiological adaptation of the hypothalamic-pituitary-adrenal axis to chronic stress.

There is a growing interest in examining biological correlates of posttraumatic stress disorder (PTSD), both as a means of obtaining relevant diagnostic information and for the purpose of more clearly understanding the pathophysiology of this disorder. Preliminary studies to date have provided evidence for disturbances in both the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Work in our laboratory, for example, has shown that combat PTSD patients have sustained elevations of 24-hour urinary catecholamine levels compared with patients in other diagnostic groups (Kosten et al., 1987) and decreased numbers of alpha$_2$ adrenergic receptors on platelets compared with nonpsychiatric control subjects (Perry et al., 1987). Consistent with these findings, other laboratories have shown that combat PTSD patients exhibit exaggerated sympathetic responses to reminders of war trauma (for review, see Kolb, 1987), and that administration of nonselective noradrenergic activating agents, such as lactate, elicit hyperdynamic sympathetic and PTSD symptoms in war veterans (Rainey et al., 1984). There is also evidence that PTSD symptoms can be reduced by medications that can affect noradrenergic activity (Frank et al., 1988).

The nature of hypothalamic-pituitary-adrenal dysfunction in PTSD is less clear. Our own observations have suggested that PTSD patients have chronically lower mean 24-hour urinary cortisol excretion than patients with major depressive, bipolar manic, or undifferentiated schizophrenic disorders (Mason et al., 1986). On the other hand, Smith et al. (1989) recently observed blunted adrenocorticotropic hormone (ACTH) responses to corticotropin-releasing factor (CRF) infusion and a tendency toward elevated baseline p.m. plasma cortisol levels in PTSD patients compared with normal control subjects. Two laboratories have reported normal cortisol responses to dexamethasone in PTSD (Kosten et al., 1988; Kudler et al., 1987).

In the present study, we set out to extend our previous pilot 24-hour urinary cortisol excretion findings in a larger sample: first, because decreased cortisol secretion in PTSD is somewhat counterintuitive given the well-known relationship between HPA activation and acute stress; second, because other investigators have not reported evidence for decreased basal pituitary-adrenal activity in this disorder. Furthermore, it was of interest to determine whether cortisol levels in PTSD subjects would be significantly lower than in normal control subjects and to assess the extent to which factors such as psychiatric hospitalization, comorbidity with major depressive disorder (MDD), and severity of other clinical symptoms are related to cortisol levels. Thus, in the present study, 24-hour urinary cortisol excretion was assessed in both inpatients and outpatients with PTSD and then related to psychiatric symptomatology.

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Methods

Sixteen nonmedicated male combat veterans (15 Viet Nam, one Korean) with PTSD and 16 age-comparable nonpsychiatric male control subjects (mean ± SD = 41.6 ± 6.0 for PTSD group, 42.1 ± 10.9 for control group) gave written informed consent to participate in the study. Routine urine toxicology screening confirmed that subjects were free of psychotropic drugs or illicit substances at the time of sample collection. Nine of the subjects were inpatients at the West Haven Veterans Hospital, and seven were outpatients recruited from the New Haven Veterans Outreach Center.

Combat exposure was rated on a scale of 1 to 14 using the Combat Exposure Scale (U.S. Government Printing Office, 1981) with scores ranging from 7 to 14 (moderate to heavy exposure) in our sample. PTSD was diagnosed using the Structured Clinical Interview for the DSM-III-R (Spitzer et al., 1987). Other diagnoses were made according to Research Diagnostic Criteria (Spitzer et al., 1987) using the Schedule for Affective Disorders and Schizophrenia interview (Endicott and Spitzer, 1978). Subjects with major medical illness, organic brain syndrome, or any psychotic disorder including schizophrenia and bipolar disorder were excluded from study. Patients with substance abuse or psychotropic medication use within the preceding 2 weeks were also excluded.

Urine samples were collected and stored frozen during the collection day on dry ice to assure stability of cortisol. This method of collection prevents the artificially high values that can occur when urine is preserved in strong acid. Sampling in both experimental and control groups was avoided during the week of admission to the hospital, on days of unusual physical activity or stress, and also during periods when unusual procedures, including endocrine challenge tests, were being performed. Completeness of collections was monitered by nursing staff for the inpatients and by determination of urinary creatinine excretion for all patients and control subjects. Mean creatinine excretions ranged from .8 to 1.9 g/day, which is within the normal range (Mason et al., 1986). For the determination of cortisol, untreated aliquots of urine were thawed, and free cortisol was extracted and analyzed using a radioimmunoassay kit procedure developed by Clinical Assays, Inc. (Cambridge, MA). Biochemical determinations were carried out with the experimenter unaware of the subject's group membership. The interassay coefficient of variation for this method was 4.0%.

Psychiatric symptomatology was assessed in the patient group using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) at the termination of the 24-hour collection. In the outpatient group, severity of PTSD symptoms was assessed using both the Impact of Events Scale (IES; Horowitz et al., 1979) and the Figley PTSD interview (Figley and Stretch, 1980).

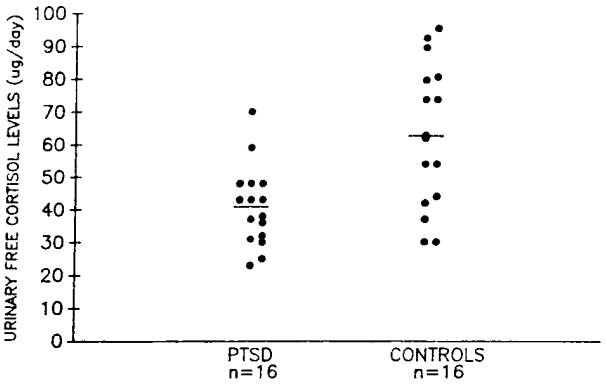

FIG. 1. Mean 24-hour urinary cortisol values for 16 PTSD patients and 16 normal control subjects.

Results are expressed as mean ± SD, with significance of the differences between patient and control groups measured by Student's *t*-test.

Results

As illustrated in Figure 1, 24-hour urinary cortisol excretion was significantly lower in the PTSD group compared with the control group (40.9 ± 12.3 μg/day, PTSD group; 62.8 ± 22.2 μg/day, control group; t = 3.4; df = 30; $p < .001$), but within the normal range. However, cortisol concentrations in inpatient and outpatient groups were not significantly different (43.3 ± 14.8 μg/day, inpatients; 37.7 ± 8.0 μg/day, outpatients).

There were also no differences in cortisol levels when the patient group was subdivided into those with (N = 8) and without (N = 8) a comorbid major depressive disorder (40.0 ± 15.5 μg/day, patients with MDD; 41.9 ± 8.7 μg/day, patients without MDD). It should be mentioned, however, that there was a significantly higher incidence of comorbidity of depression in the inpatient compared with the outpatient group (6 of 9 inpatients compared with 2 of 7 outpatients).

Correlational analysis failed to reveal a significant relationship between 24-hour urinary cortisol excretion and total BPRS scores in the patient group as a whole (r = .22; NS), or when inpatients and outpatients were considered separately (r = .04, NS, inpatients; r = .26, NS, outpatients). However, inpatients were almost twice as symptomatic as outpatients as measured by total BPRS scores (22.3 ± 6.7 inpatients compared with 12.1 ± 6.8 outpatients (t = 2.99; df = 15; $p < .01$). This was primarily in the areas of anxiety, depression, and tension. In the outpatient

group, there was a trend for a relationship between cortisol excretion and overall PTSD symptoms as measured on the IES (r = .64; NS) and Figley (r = .43; NS).

Discussion

The present findings provide further evidence for a reduced pituitary-adrenal activation in chronic PTSD. The mean urinary-free cortisol excretion in the PTSD group was similar to our previously published value (Mason et al., 1986) and significantly lower than normal control levels. Furthermore, the range of cortisol excretion was narrower in the patient group. In contrast to single or even multiple plasma sampling, a 24-hour urine collection accurately reflects total daily cortisol output, which consists of both diurnal and stress-induced cortisol secretion. In the only other reported study that measured cortisol levels (Smith et al., 1989), there was a nonsignificant trend for PTSD patients to have an elevated p.m. baseline cortisol concentration. However, in this case differences in cortisol may have been difficult to detect in a single p.m. plasma sample, especially at a time when cortisol levels are typically at their nadir in the circadian cycle.

In attempting to understand the possible significance of low urinary cortisol in PTSD, it is important to note that, despite the overall trend for cortisol suppression in this group, all values appeared to be in the endocrinologically defined "normal" range. Furthermore, there was considerable overlap in hormonal values between patients and normal control subjects. Thus, rather than suggesting glandular abnormalities in PTSD, the attenuated basal hormone levels within the normal range suggest changes in central modulatory processes (Mason et al., 1989).

Low cortisol has been associated with chronic, but not acute, stress and has been documented in humans (Bourne et al., 1967, 1968; Mason et al., 1990), nonhuman primates (Mason, 1968), and rodents (Levine, 1962). This phenomenon is not thought to be associated with adrenal exhaustion, as superimposed acute stress is capable of increasing glucocorticoid secretion in chronically stressed animals (Mason, 1968; Mason et al., 1990). The lower cortisol excretion we have observed in PTSD may reflect a disturbance in stress-induced HPA activation, which may be conceptualized either psychologically or physiologically. For example, cortisol suppression may be related to the use of defense mechanisms such as denial or paranoia (Mason et al., 1986; Wolff et al., 1964a, 1964b), both of which can be present in PTSD. Chronic stress may also lead to a physiological adaptation (Levine, 1962) in the form of a heightened negative feedback sensitivity at the level of the hypothalamus or pituitary. An increased feedback sensitivity could hypothetically lead to a decreased synthesis and release of corticotropin-releasing factor and/or adrenocorticotrophic hormone. Given that investigators have reported changes in glucocorticoid receptor number in response to both glucocorticoids and stress (Meaney et al., 1985; Sapolsky et al., 1984), this physiological adaptation to stress could involve an altered regulation of glucocorticoid receptors at the feedback sites of the HPA (Yehuda et al., 1989).

An altered negative feedback sensitivity within the HPA axis has been postulated in MDD (Gold and Chrousos, 1985; Gold et al., 1986; Holsboer et al., 1984). In this case, feedback sensitivity is decreased, paralleling a decrease in glucocorticoid receptor number measured in lymphocytes (Gormley et al., 1985; Whalley et al., 1986). MDD has also been associated with hypercortisolemia (Gold and Chrousos, 1985; Gold et al., 1986; Holsboer et al., 1984; Sachar et al., 1973). Of note, in the present study, cortisol excretion was also low in PTSD patients with a concurrent diagnosis of MDD, suggesting that depression experienced in PTSD may have a distinct pathophysiology from that of MDD occurring without PTSD.

While the above hypothetical model suggests that some physiological adaptation is associated with the chronic stress of PTSD, the long-term effects of glucocorticoid suppression in response to chronic stress may be detrimental. Glucocorticoids initiate the suppression of metabolic, immune, and neural defensive reactions that normally occur in response to stress; the failure of the HPA axis to respond to stress by increasing circulating glucocorticoids has been associated with potentially deleterious consequences such as tissue damage (Munck et al., 1984). In patients with PTSD, there may be other consequences associated with a suboptimal stress-induced glucocorticoid secretion. For example, low cortisol may be associated with the increased norepinephrine output observed in the PTSD patients (Kosten et al., 1987). This hypothesis would be consistent with recent observations of low cortisol and increased norepinephrine in chronically stressed animals (Irwin et al., 1986; Mason, 1968).

The interaction of cortisol with other hormones and neurotransmitters is an important area for future research in PTSD (Yehuda et al., 1990). Our previous work has strongly suggested that the role of hormones in psychiatric disorders is best conceptualized not in terms of a single neuroendocrine system in isolation, but rather in terms of the balance or overall organization of multiple hormonal and neurotransmitter systems, which exert interdependent effects at the cellular levels (Mason et al., 1989). Thus, the further characterization of HPA abnormalities in PTSD in conjunction with explorations of other neuroendocrinological systems may be of great value in elucidating the pathophysiology of this disorder.

Finally, it is important to address the relationship of clinical symptomatology to the present biological

findings. Although no significant correlations between cortisol secretion and psychiatric symptomatology could be observed in the overall sample, group differences in sum BPRS scores were present between inpatients and outpatients with PTSD. This difference likely reflects the greater degree of depression in the inpatient group or the fact that individuals with PTSD requiring hospitalization are generally more symptomatic overall than those who seek outpatient therapy. Outpatients in our sample with PTSD, however, were quite distressed, as shown by Figley and IES scores. In this latter group, severity of PTSD symptoms did seem related to cortisol excretion. In the aggregate, however, the low cortisol observed independent of overall psychiatric symptomatology suggests that low cortisol in PTSD is a relatively stable characteristic of this disorder.

Conclusions

Mean 24-hour urinary cortisol excretion was significantly lower in both inpatients and outpatients with PTSD compared with nonpsychiatric control subjects. Despite some observable relationships between severity of PTSD symptomatology and cortisol in the outpatient group, low cortisol in PTSD was not related to the presence or absence of specific comorbid conditions or general "state" psychiatric symptomatology; instead, low cortisol seems to represent a stable characteristic of individuals suffering from this disorder. The results provide encouragement for further exploration of hypothalamic-pituitary-adrenal dysfunction in PTSD.

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